Exhibit 3

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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| IN RE APPLICATION OF: Gerald L. Mechanic | § | DOCKET NO.: BIOC,002/CIP |
| SERIAL NO.: 07/557,639 | § | GROUP ART NO.: 112 |
| FILED: July 30, 1990 | § | EXAMINER: I. McAndrews |
| FOR: PROCESS FOR CROSS-LINKING COLLAGENOUS MATERIAL AND RESULTING PRODUCT | § | |



**RESPONSE TO OFFICIAL ACTION OF SEPTEMBER 14, 1990**

The Honorable Commissioner
of Patents and Trademarks
Washington, D.C. 20231

Sir:

Applicant responds to the Official Action of September 14, 1990 as follows. A request for a three month extension of the time to respond to that Action, and a check for the required fee, is enclosed. In the event that the request is inadvertently not enclosed, or that the check is not enclosed or is insufficient in amount, request is hereby made for an extension of the time to respond for a period of time sufficient to insure that the response is made in timely fashion, and the Commissioner is authorized to charge any fees or insufficiency to Deposit Account No. 22-0020 (BIOC,002/CIP).

IN THE CLAIMS

Amend the following claims:

1. (Amended) A process for cross-linking [collagenous materials] collagen fibrils comprising the steps of:

~~incubating~~ a sample of [collagenous material] collagen fibrils to be cross-linked in an aqueous media

solution of a photooxidative catalyst buffered to a pH of from about 6.8 to about 8.6 for a period of time sufficient to allow equilibration of the concentrations of media solution, [collagenous material] collagen fibrils, and catalyst and

irradiating the [collagenous material] equilibrated collagen fibrils with light in the presence of oxygen for a period of time sufficient to cross-link the [collagenous material] collagen fibrils by transfer of electrons from catalyst to [collagenous material] collagen fibrils while maintaining the temperature of the media solution at between about -2 and about 40°C.

Claims 5 and 6, line 1 of each claim, change "collagenous" to --collagen--; line 2 of each claim, change "materials" to --fibrils--.

9. (Amended) A process for cross-linking [proteinaceous material] the collagen fibrils of a collagenous tissue comprising the steps of:

soaking a collagenous tissue sample [of a proteinaceous material] in an aqueous medium having a high osmolality;

incubating the soaked collagenous tissue [proteinaceous material] in an aqueous buffer including a photooxidative catalyst capable of donating electrons to the amino acids comprising the collagen fibrils of the collagenous tissue [proteinaceous material] when exited by incident light to form inter- and/or intra-molecular cross-links; and

irradiating the collagenous tissue [proteinaceous material] in the aqueous buffer including the catalyst with light while [holding the temperature and pH of the aqueous buffer at levels sufficient to maintain] maintaining the oxygen concentration of the aqueous buffer so as to sensitize the catalyst into an excited state which is reduced by oxidative cross-linking of the amino acids of the [proteinaceous material] collagenous tissue, the pH being maintained at between about 6.8 and about

8.6 and the temperature being maintained at between about -2 and about 40°C.

Claim 15, line 1, change "proteinaceous" to --collagenous--.

Add the following new claims:

~~16~~. A process for cross-linking collagenous material comprising the steps of:

soaking a sample of collagenous material to be cross-linked in an aqueous buffer solution having an osmolality of from about 393 to about 800 mosm;

~~incubating~~ the soaked collagenous material in an aqueous media solution of a photooxidative catalyst buffered to a pH of from about 6.8 to about 8.6 for a period of time sufficient to allow equilibration of the concentrations of media solution, collagenous material, and catalyst, and

irradiating the ~~equilibrating~~ collagenous material with light while maintaining the oxygen concentration of the media by maintaining the oxygen concentration of the atmosphere above the media at from greater than about 0 up to about 25% for a period of time sufficient to cross-link the collagenous material by transfer of electrons from catalyst to collagenous material while maintaining the temperature of the media at between about -2 and about 40°C.

17. The process of claim ~~16~~ wherein the pH is maintained in the range of from about 7.4 to about 8.0.

~~18~~. The process of claim ~~16~~ wherein the oxygen concentration of the media during irradiation is maintained by maintaining the oxygen concentration of the atmosphere above the media at from about 5 to about 20%.

~~19~~. The process of claim ~~16~~ wherein the collagenous material is irradiated with a range of between about 100 and about 20,000 lumen hours.

~~20~~. The process of claim 16 wherein the temperature is maintained at between about 0 and about 25°C.

REMARKS

In the Official Action of September 14, 1990, claims 9-15 were rejected on obviousness-type double patenting grounds over claims 14, 15, and 17-20 of co-pending application Ser. No. 07/388,003 (now abandoned in favor of a continuation application, Ser. No. 07/651,099) over the Kuntz patent. Claims 1, 2, 5, 6, and 8 were rejected as being anticipated by the Kuntz patent, and claims 3, 4, and 7 were indicated as having been objected to solely because they depended on rejected claims. In light of that indication with respect to claims 3, 4, and 7, new claim 16 has been added which incorporates the recitations of claims 1, 3, 6, and 7 (7 having been dependent on 6), thereby introducing an allowable claim into the application. Claims 17-20 are dependent on new claim 16 (claim 18 is similar in content to claim 4) and are, therefore, also in condition for allowance. It is respectfully requested that the following remarks, made in accordance with the requirements of 37 C.F.R. §§1.111(b) and (c) and 1.119, be considered with respect to the other rejections of record.

The double patenting rejection of claims 9-15 over the combination of Kuntz and claims 14, 15, and 17-20 of the co-pending application is respectfully traversed, but with some qualifications. Indeed, the rejection is arguably appropriate and Applicant fully intends (most likely as soon as all §112 rejections are withdrawn in the parent application) to either combine the claims of the co-pending parent application (now Ser. No. 07/651,099) with this application, cancel claims from one application or the other, or otherwise take action to remedy this situation. However, the basis for this rejection set out in the Official Action of September 14, 1990 is improper, and it is for this reason that the rejection is traversed.

Specifically, it is the assertion that it is well known, as exemplified by col. 12, lines 23-28 and col. 6, lines 53-64 of Kuntz, to dissolve proteinaceous material in water which is the basis for this traversal. Attention is respectfully directed to the amendment to claim 9 set out above so that the

claim now recites that it is the collagen fibrils of a collagenous tissue which are soaked, incubated, and irradiated rather than a "proteinaceous material". This amendment is important for at least two reasons with respect to this rejection:

(1) contrary to the assertion set out in the Official Action, true native collagen fibrils cannot be solubilized in water or aqueous solution (even before they are cross-linked in accordance with the method of the present invention), and

(2) Kuntz does not teach the cross-linking of native collagen fibrils; neither the product of the Kuntz process nor any of the collagenous materials that were used in that process are native collagen fibrils in spite of the many references in the specification of that patent to "intact collagen fibrils", "native collagen" and "reconstituted" fibrils.

Applicant is presently preparing the Rule 132 Declaration of David Cheung, Ph.D. which will set out the evidence supporting these two statements so that they will not be regarded as mere arguments of counsel. By way of introduction (and emphasis), however, and to serve as a basis for that discussion in the Cheung Declaration, native collagen fibrils have a specific structure which causes the individual collagen molecules to align in such a way that the fibril is referred to as being a "quarter-staggered array". Attached hereto as Exhibit A are pages 132-135 of the Ninth Edition of Bloom and Fawcett's definitive reference work, A Textbook of Histology (W.B. Saunders Company: Philadelphia 1968) providing further explanation of the structure of a collagen fibril and showing why the structure of the collagen fibril is described as being quarter-staggered. As will be made clear in the Cheung Declaration, neither the product of the Kuntz process not any of the collagenous materials that were used during that process are native collagen fibrils having this quarter-staggered configuration in spite of the many statements to

that effect in the specification of Kuntz. They are instead collagen molecules, or as referred to in Bloom & Fawcett (Exhibit A), tropocollagen molecules (which can form quarter-staggered collagen fibrils under certain conditions, none of which are present in Kuntz). In considering the importance of this difference between the disclosure of the Kuntz patent and Applicant's process, it is respectfully requested that it be noted that Applicant has not simply argued this point in this Response; instead, specific amendments has been made to claim 1 to recite that it is the collagen fibrils of a collagenous tissue, not collagen molecules, which are cross-linked in accordance with Applicant's method.

For this very basic reason, it is requested that this double patenting rejection be reconsidered. Although withdrawal of this rejection is not necessarily solicited in light of the co-pending application, withdrawal of the basis for the rejection is requested in light of these remarks and the evidence which is presently being prepared for submission in the case.

Turning now to the §102 rejection of claims 1, 2, 5, 7, and 8 over Kuntz, that rejection is also respectfully traversed in light of the amendments set out above which specify that it is collagen fibrils which are cross-linked and the evidence to be submitted that Kuntz does not disclose the cross-linking of collagen fibrils. However, the lack of a disclosure in Kuntz of the cross-linking of collagen fibrils is not the only difference between Applicant's claimed process and the Kuntz process. For instance, at col. 5, lines 54 *et seq.* of the specification of Kuntz, it is stated that the pH during irradiation may vary from 2.0 to 14.0. As will be made clear by the discussion of the effects of acid on collagen fibrils that will be set out in the Cheung Declaration, a pH below neutral (about 7.0) jeopardizes the integrity of the collagen fibrils. Consequently, Applicant's claim 1 recites that the collagen fibrils are soaked in a medium "buffered to a pH of from about 6.8 to about 8.6" (e.g., a pH which does not denature the collagen fibrils) for photooxidation. As will

be further developed in the Cheung Declaration, in the case of the process described in Kuntz, the fibrils were already denatured (e.g., they were no longer fibrils) such that it did not matter whether the irradiation was conducted in acid pH.

Another difference between the Kuntz disclosure and Applicant's claim 1 is the lack of any mention in Kuntz of the necessity of oxygen, as recited in claim 1, and the relationship between the presence of oxygen and the oxidation reaction which occurs. Reference is made to col. 2, lines 12-19 of the specification of Kuntz, at which a mechanism is postulated for the photooxidative cross-linking reaction described in that patent which actually teaches away from the recitation of the presence of oxygen in Applicant's claim 1 because it postulates the "extraction" of electrons from the amino acids of the collagen fibrils by the dye. The presence of oxygen is recited in Applicant's claim 1 because it appears that the oxygen forms a complex with the dye which then oxidizes the amino acids of the collagen, all as set out at page 9, line 33 - lines 10, line 8 of the specification of the present application. In other words, electrons are transferred to the amino acids of the collagen molecules instead of from them as taught by Kuntz. It is, of course, well established that a reference which teaches away from the claimed invention not only does not render that invention obvious but it actually augurs for the patentability of that invention. In re Dow Chemical Co., 5 U.S.P.Q.2d 1529, 1532 (Fed. Cir. 1988). It is submitted that the §102 rejection of claim 1 is inappropriate for this reason alone, and should be withdrawn.

Some additional differences between Kuntz and Applicant's claim 1 are as follows. Throughout the specification of Kuntz, repeated references are made to the "shaping" of the cross-linked gel described in that patent to make a "shaped article" (col. 4, line 6) such as a film, fiber, or sponge. For instance, at column 3, lines 35-44, the specification of that patent describes

> "...the preparation of a collagenous gel in which the collagenous substance...is converted to a polymerized, cross-linked form by exposing an acid dispersion of the

> collagenous starting material to irradiation in the presence of a photo-sensitized dye. The gel of polymerized collagenous material is then shaped to the desired form, e.g., [by] evaporation, neutralization or dehydration."

It is, of course, the existence of this "gel of polymerized collagenous material" which permits such shaping in the sense that a gel has physical characteristics which allow it to be shaped. In this respect, the Kuntz process if very different from Applicant's process, which does not involve any shaping at all and which, although it results in a product which can be shaped by subsequent operations, effectively starts with a solid and ends with a solid, not a gel. Attention is respectfully directed to Examples 4-7 of the present application, which describe the use of the process claimed in claim 1 on a tissue including collagen fibrils, and which result in a tissue including stabilized cross-linked collagen fibrils, helping to illustrate this difference between Kuntz and Applicant's claimed invention.

Another difference between Kuntz and the present invention again relates to pH conditions. Just like the acid pHs recited at column 5, lines 54-63 of Kuntz are inappropriate for use in Applicant's claimed invention (such that claim 1 recites that the collagen fibrils are soaked in a medium buffered to a pH between about 6.8 and about 8.5 so as not to denature them), so also do the alkaline pHs recited at that point in Kuntz (note that a pH of 5.0 as recited in line 62 of Kuntz is not alkaline in the first place). True native (e.g., quarter staggered collagen fibrils are not stable for any significant period of time at pH 9.0-14.0 because desamidation of the collagen protein occurs at these higher pH values, resulting in the formation of free carboxyl groups. These carboxyl groups repel each other, causing the fibrils to swell and start unraveling, and the longer they are maintained in alkaline pH conditions, the more they unravel. These facts were known at the time Kuntz prepared her patent application (see, for instance, K. Gustatson, The Chemistry and Reactivity of Collagen, Academic Press: New York 1956; Applicant will be pleased to supply a photocopy of this references if necessary

to avoid the treatment of these remarks as unsupported arguments of counsel). Therefore, those skilled in the art would be justified in concluding that, if Kuntz knew about the effect of alkaline pH values on collagen fibrils, but nevertheless specified the use of such pHs, she must not have been working with collagen fibrils. The significance of this conclusion is clear from the fact that desaminated collagen loses its ability to form native, quarter-staggered collagen fibrils. K. Kuhn, et al., 1 Chemistry and Molecular Biology of the Intercellular Matrix 43, 251 (1970). This difference represents another reason why Applicant's claim 1 has now been amended to recite that it is collagen fibrils which are cross-linked.

Before concluding, it is respectfully requested that the differences in the results reported in the specification of the Kuntz patent and the present application be noted. Although more relevant to the obviousness rejection of record ("An analysis of obviousness of a claimed combination must include consideration of the results obtained by that combination". Gilette Co. v. S.C. Johnson & Son, Inc., 16 U.S.P.Q.2d 1923, 1928 (Fed. Cir. 1990)), in light of the claim amendments set out in the Response to specify that it is the collagen fibrils which are cross-linked by Applicant's process, it is suggested that the difference in results can now be better appreciated. Specifically, Kuntz reports (see, for instance, Example VII) that the allegedly cross-linked product of that process is digested faster that the uncross-linked starting material by the mildly proteolytic enzyme papain when more completely cross-linked by longer periods of irradiation. That result is exactly the opposite of the claimed method, in which irradiation causes the cross-linked product to be considerably less susceptible to digestion by proteolytic enzymes (and even the highly destructive enzyme, bacterial collagenase) than the starting material. In light of this difference and the amendments and remarks set out above, reconsideration and withdrawal of the rejections, allowance of

the claims, and passage of the application to issuance PAT respectfully requested.

Respectfully submitted,

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Dated: March 14, 1991

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